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THE ASSAY, CHARACTERISTICS, COMPOSITION, AND ORIGIN OF OPIUM

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The Determination of morphine in raw opium

by Dr. Erich Knaffl-Lenz

In continuation of the international programme of scientific research on opium, undertaken pursuant to Resolution 246 F (IX) adopted by the Economic and Social Council on 6 July 1949, and the decision of the Commission on Narcotic Drugs at its fifth session, calling for further study of the assay of opium, the Secretary-General is now publishing a method for the determination of morphine in opium, as worked out by Dr. Erich Knaffl-Lenz, former Expert for the Opium Committee of the Health Section, League of Nations.

The Secretary-General wishes to call attention to the following features of the method: preliminary defatting of the opium; total extraction with neutral hot water; and precipitation of troublesome impurities by saturation with sodium sulfate. The method is one of extraction of the morphine by organic solvents; it is not a precipitation method.

THE DETERMINATION OF MORPHINE IN RAW OPIUM

By Dr. Erich Knaffl-Lenz, formerly Expert for the Opium Committee of the Health Section, League of Nations, and Reporter of the Opium Committee of Experts, Office Internationale d'Hygiene publique, Paris

Principle of the method

The preparation of an aqueous extract is made as follows: a part of the content of fats and resins is removed from the opium by means of carbon tetrachloride or a similar fat-dissolving solvent, after which the alkaloids are extracted by neutral hot water, and finally most of the troublesome impurities are precipitated out by saturating the solution with sodium sulfate. Extraction by means of acidified water is not suitable, because the narcotine is also dissolved, the porphyroxine is decomposed with the formation of a red coloring material, and in addition a much greater quantity of impurities goes into solution.

The separation of the morphine from the secondary alkaloids is effected by the addition of a carbonate-free sodium hydroxide solution, by means of which the alkaloids other than morphine and narceine are precipitated. The small quantity of codeine remaining in solution is removed by means of benzene.

The morphine is then liberated from solution by the addition of sodium bicarbonate, and shaken out with a warm mixture of chloroform-ethanol. Since the solubility of ethanol in the saturated sodium sulfate solution is slight, it is quite feasible to obtain the morphine quantitatively, using only small quantities of solvent. The combined extracts are dehydrated with anhydrous magnesium sulfate, then evaporated to dryness, and the morphine residue is then titrated with tenth-normal hydrochloric acid, using methyl red as indicator. When necessary a further purification to lessen the brown colour is made, as described below.

Insofar as the purity of the morphine is concerned, numerous methoxyl determinations have never yielded more than 0.05% of methoxyl, presumably due to a content of narceine, which would be unimportant, since it would not be titrimetrically determined.

This method has the advantage over the usual lime methods of the present time in that the opium is quantitatively extracted, so that neither correction factor nor extract determination is necessary. Moreover, a determination can readily be made in two or three hours.

/Description

Description of the method

3.00 grammes of finely powdered opium, dried at 105° C. are mixed with 20 cc C Cl_4 in a small wide-mouthed Erlenmeyer flask, until a slurry is formed. This is warmed on the water bath with frequent agitation, then poured into a Jena glass sinter filter number 3G3, which has on it a double layer of filter paper, and filtered with suction. The opium is washed twice, each time with 5 cc warm C Cl_4, then air is drawn through long enough for the C Cl_4 to be evaporated.

The dry opium is then brought back into the flask as completely as possible, which can best be done by lifting off the filter paper. It is then treated with 20 cc water, and heated for at least 5 minutes on the steam bath, while being frequently shaken. After this, 2.8 gm Na_2SO_4 are added and dissolved, and the whole is cooled and allowed to stand for at least 20 minutes.

The separation of the opium residue from the aqueous extracts can be carried out either by means of a glass-sinter filter or by centrifuging. In the latter case, however, the centrifugally separated opium residue must be washed onto a filter with 5 cc of saturated Na_2SO_4 solution. The filtration proceeds much more quickly if a small quantity of sea sand is added, which prevents the opium residue from sticking together. When the sinter filter is used it is covered with filter paper, and the liquid is drawn through with slight suction and the residue washed with 5 cc saturated Na_2SO_4. Following the first filtration the opium residue is sucked dry and returned to the flask once more, 20 cc saturated Na_2SO_4 poured over it, and the process just described is repeated.

3 cc 5 n NaOH are added to the filtrate. Another extraction of the opium residue is made with 15 cc Na_2SO_4 solution, and the residue washed with enough sulfate solution to bring the combined filtrates to 75 cc. Most suitable for this filtration is a cylindrical vessel having its upper third constricted to 1 cm diameter, and having markings up to 75 cc. The glass filter is placed over this vessel with a two-holed stopper, the second hole serving as the means of connecting the apparatus with a water-jet vacuum pump.

The combined filtrates, together with the NaOH, are vigorously shaken together, and then after standing 20 minutes, filtered through a folded filter paper into a cylindrical separatory funnel containing 100 cc of warm benzene. This separatory has a total capacity of 200 to 250 cc and is constricted for about 4 cm of its length in the middle to 1 cm. When at least 55 cc of the extract have been filtered through, the separatory is stoppered and then turned

/several times

several times about its axis. This manner of shaking out avoids the formation of troublesome emulsions. The codeine in the solution passes into the benzene.

50 cc of the benzene-extracted solution (corresponding to 2.5 gm of opium) are shaken out for morphine in a separatory funnel of the kind just described. The first shake-out is made with 75 cc of a 3:2 chloroform-ethanol mixture, after adding 15 cc of 8% $NaHCO_3$ solution.

It is advisable to warm the separatory funnel before use by running warm water through it, and also to use warm mixtures, in order to prevent the crystallizing out of Na_2SO_4. If some does crystallize out, it can be dissolved by the addition of a little warm water.

The second shake-out is carried out with 50 cc of 3:1 chloroform-ethanol and the third with 20 cc (3:1). The Marquis reaction can be used to determine the completion of the shaking out.

If small quantities of emulsion should form, it is advisable to draw it off into a small flask, where it can be treated with dry $MgSO_4$, and the filtrate can then be combined with the other shakeouts.

The combined shakeouts are dried by shaking with anhydrous $MgSO_4$, filtered into a small distilling flask, and evaporated to dryness.

If the dry residue is not too dark in colour it can be titrated using methyl red indicator with tenth-normal hydrochloric acid. By multiplying the number of cc of acid used by the factor 1.426 the percentage content of morphine is obtained.

In a number of types of opium the brown colouring matter hinders the titration, in which case the morphine residue is dissolved in the least possible amount of acid, then diluted with 20 cc of saturated Na_2SO_4 solution, and after setting the morphine free it is again shaken out.

Often it suffices to recrystallize the morphine residue as follows: dissolve by warming with 2 cc methanol-benzene (1:3), then add 10 cc of saturated morphine solution, let cool, and after half-an-hour's standing carefully remove the liquid, in which most of the colouring matter remains dissolved, by means of a glass tube drawn out into a capillary. However, the colouring is usually of importance only when larger quantities of opium are used for analysis.

/Comparative Analytical Results

Comparative Analytical Results

Method	Samples				
	Benares	Calcutta	Iran	Turkey	Yugoslavia
Kraffl-Lenz	11.86	11.14	12.08	12.10	16.70
Kier-Wackerlin	11.84	11.27	12.09	12.12	16.62
Harrison and Self	10.47	9.99	11.56	11.46	16.27
International	11.00	10.35	11.52	12.03	16.57

The first two methods give identical values, without the use of a correction factor, whereas the other methods give lower values despite the use of a high correction factor (10 to 16%).

Reagents

1. Anhydrous sodium sulfate.
2. Anhydrous magnesium sulfate.
3. Saturated sodium sulfate solution.
4. 8% sodium bicarbonate solution.
5. Saturated morphine solution.

Preparation: Gradually pour 10 cc of a hot ethanol solution saturated with morphine base into 1 liter of boiled distilled water, with constant stirring and shaking, and after it has been allowed to stand 24 hours, decant the solution from the morphine crystals and keep it in a dark container.

6. 5 normal carbonate-free sodium hydroxide.
7. Chloroform-ethanol mixtures:

   3:2, specific gravity 1.220
   3:1, specific gravity 1.300

The mixtures distilled off can be brought to the right proportions again by adding suitable quantities of ethanol.

8. Benzene.
9. Methanol-benzene, 1:3.
10. Methyl red solution. A solution of 0.05 gm methyl red in 75 cc ethanol is diluted to 100 cc with boiled distilled water.
11. Sea sand, previously cleaned with hydrochloric acid.
12. Carbon tetrachloride.